DOCKET NO.: AM100299 P2 (WYNC-0677) **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Adam M. Gilbert and Gary P. Stack **Confirmation No.: 3576**

Application No.: 10/663,533 **Group Art Unit: 1625**

Filing Date: September 16, 2003 **Examiner: Evelyn M. Huang**

For: 8-AZA-BICYCLO[3.2.1]OCTAN-3-OL DERIVATIVE OF 2,3-DIHYDRO-1,4-BENZODIOXAN AS 5-HT $_{1A}$ ANTAGONISTS

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF REPLY BRIEF PURSUANT TO 37 CFR § 1.193

Transmitted herewith in triplicate is the REPLY BRIEF in this application with respect to the Examiner's Answer dated **July 11, 2005**.

If any fee is required, please charge Deposit Account No. 23-3050. A duplicate of this transmittal is attached.

Date: September 12, 2005

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Sir:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 1.193

Appellants submit this Reply in response to the Examiner's Answer dated July 11, 2005 in connection with the above-identified application. This reply is being filed within two months of said answer.

The evidence of record establishes that the application as filed as combined with the knowledge of those skilled in the art enables the appealed claims pursuant to 35 U.S.C. § 112, first paragraph, and Appellants respectfully submit that the U.S. Patent and Trademark Office ("Office") has failed to proffer sufficient basis for questioning this evidence or otherwise reaching a contrary conclusion.

First, assuming *arguendo* that the Office is correct in stating that a high level of unpredictability is recognized with respect to the 5-HT receptor ligand art, Appellants submit that the Office improperly asserts that this necessarily means that the provided *in vitro* binding data does not reflect the *in vivo* activity of the inventive compounds. The

predictability or unpredictability of the art does not absolutely inform the inquiry into whether *in vivo* data may be predictive of *in vivo* activity. According to the Federal Circuit, what reliably informs this inquiry is whether the necessary correlation between *in vitro* and *in vivo* assays is recognized and accepted among those skilled in the art (*see In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (reversing the PTO decision based on its finding that *in vitro* data did not support *in vivo* applications)), and Appellants have demonstrated that representative compounds of formula I *do* have 5-HT_{1A} serotonin receptor antagonist activity through two art-recognized assays. *See* Appellant's Brief at page 8. The Office does not provide any other reason for its conclusion that there is insufficient correlation between the *in vitro* and *in vivo* models, and accordingly Appellants submit that the Office so has not met its burden to provide reasons for the alleged lack of enablement in this respect. *See* MPEP 2164.02.

Since the disclosed assays represent reliable means for confirming the $5HT_{1A}$ serotonin receptor antagonist activity of the disclosed compounds, to overcome the rejection under 35 U.S.C. § 112, first paragraph, Appellants needed only demonstrate that those skilled in the relevant art recognize the nexus between $5HT_{1A}$ antagonism and the treatment of Alzheimer's disease, appetite disorders, disorders of thermoregulation, and sleep dysfunction.

Alzheimer's disease

The Office incorrectly asserts that the Schechter reference was published after the effective filing date of the application presently on appeal; that reference was published in 2002, and the effective filing date of the application that is the subject of the instant appeal is September 16, 2003. Additionally, the claims on appeal are not exclusively directed to the absolute *cure* of Alzheimer's disease; instead, the claims provide "method[s] of treating" that condition, and alleviation of one or more symptoms associated with Alzheimer's disease would constitute such treatment. Thus, Schechter's recognition that $5HT_{1A}$ receptor antagonists "[represent] a novel therapeutic approach to the treatment of cognitive deficits associated with Alzheimer's disease" demonstrates the recognition among those skilled in the art that a clear nexus exists between $5HT_{1A}$ receptor antagonism and the treatment of

Alzheimer's disease. The Lanfumey reference, which reiterates this recognition (*see* Lanfumey at page 5, col. 1), cites to Schechter.

Additionally, the Office should not have used the fact that the Lanfumey and Kwon, references were published after the effective filing date of the application presently on appeal to demonstrate that the claims on appeal are not enabling. *See* MPEP 2164.05(a). Although an exception to this rule exists for situation where the later-dated reference provides evidence of what one skilled in the relevant art would have known on or before the effective filing date, *see id.*, this exception does not apply to the instant situation; on the contrary, the Lanfumey reference, as described above, does the opposite, providing evidence that at the time of the effective filing date one skilled in the art already knew of the nexus between $5HT_{1A}$ antagonism and treatment of Alzheimer's disease. Likewise, Kwon reference demonstrates that at the time of the effective filing date of the application presently on appeal $5HT_{1A}$ receptor antagonists were known among those skilled in the art to provide effective treatment for Alzheimer's disease: Kwon provides that at the time of that article's publication, $5HT_{1A}$ receptor antagonists were undergoing phase II clinical trials, which means that phase I trials (demonstrating safety, and taking several months to a year) and pre-clinical trials (demonstrating efficacy, and taking approximately three to four years) had already been satisfactorily completed. Taking into account this timeline, it is again clear that at the time of the effective filing date of the application presently on appeal, those skilled in the art were well aware of the nexus between $5HT_{1A}$ receptor antagonism and the treatment of Alzheimer's disease.

Appetite Control

In order to expedite the resolution of the instant pending case, Appellants have separately submitted an amendment pursuant to 37 C.F.R. § 1.116 that deletes from claim 26 the method of using the described compounds to provide treatment for conditions relating to appetite control. Appellants have respectfully requested entry of the amendment, and note that the amendment reflects Appellants' continuing view that the unamended portions of the

claim are in condition for allowance. Appellants have provided in APPENDIX A a listing of the appealed claims showing changes made via an amendment pursuant to 37 C.F.R. § 1.116.

Disorders of Thermoregulation

Brubacher and Oerther together stand for the proposition that disruption of thermostasis as induced by serotonin excess in response to excessive stimulation of the 5-HT_{1A} serotonin receptor can have the net physiological effect of either hypothermia or hyperthermia. The Office's suggestion that Brubacher (demonstrating hyperthermia from 5-HT_{1A} agonism) is "at variance" with Oerther (hypothermia from 5-HT_{1A} agonism) is therefore injudicious. The relevant teaching for the purposes of this Appeal is that the role of the 5-HT_{1A} serotonin receptor in thermostasis and thermoregulation is recognized among those skilled in the art; serotonin excess as induced by 5-HT_{1A} serotonin receptor agonists directly disrupts thermoregulation. Alleviating the condition of serotonin excess can be expected to result in the parallel alleviation of the state thermoregulatory upheaval.

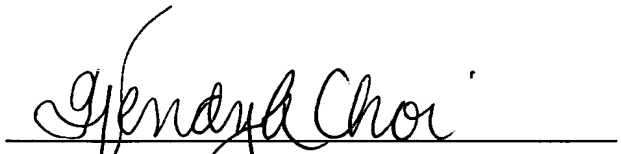
Sleep Dysfunction

The Office's citation to the first sentence in the Bjorvatn abstract is inappropriate, since in stating that the role of the neurotransmitter serotonin (5-HT) "remains controversial," the reference is merely presenting the problem that the reported study sought to address, and, in any event, later states that the results of the study "suggest that 5-HT1A receptor activation may increase waking, increase slow wave sleep or increase REM sleep." Contrary to the Office's assertion, this study, as well as the results disclosed in Gillin, would indeed suggest to one of ordinary skill in the art to "use a 5-HT_{1A} antagonist to increase wakefulness." Thus, the nexus between 5-HT_{1A} receptor antagonism and treatment of sleep dysfunction is clearly provided by the art at the time the filing of the application presently on appeal.

Appellants thus have established that the Examiner's Answer does not proffer sufficient basis for questioning the evidence presented in Appellant's Brief or otherwise reaching a contrary conclusion therefrom.

Because the rejected claims are sufficiently enabled, Appellants respectfully request that the rejection of claims 26 and 33-52 under 35 U.S.C. § 112, first paragraph, be reversed.

Date: **September 12, 2005**



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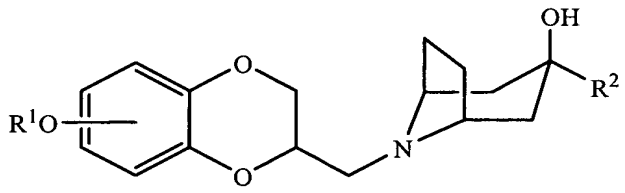
APPENDIX A:
VERSION WITH MARKINGS TO SHOW CHANGES MADE TO APPEALED CLAIMS UNDER 37 C.F.R. § 1.116

26. (***currently amended***) A method of treating a subject suffering from a condition selected from the group consisting of Alzheimer's disease, ~~appetite control,~~ disorders of thermoregulation, and sleep dysfunction, comprising the step of:

providing to the subject suffering from said condition, a therapeutically effective amount of a compound of formula I



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(I)

wherein

R^1 is a straight-chained alkyl of 1 to 6 carbon atoms, or a branched chain alkyl of 3 to 8 carbon atoms; and

R^2 is phenyl, naphthyl, anthracyl, phenanthryl, pyridyl, pyrimidyl, triazinyl, furyl, pyrrolyl, pyrazolyl, indolyl, imidazolyl, benzofuryl, benzothienyl, oxazolyl, or thiazolyl each optionally substituted with 0 to 3 substituents selected from straight-chain alkyl of 1 to 6 carbon atoms, branched-chain alkyl of 3 to 8 carbon atoms, alkoxy of 1 to 6 carbon atoms, mono- or dialkylamino of 1 to 6 carbon atoms, nitro, halo, amino, cyano, trifluoromethyl, trifluoromethoxy and hydroxy;

or a pharmaceutically acceptable salt thereof.

33. (***previously presented***) A method according to claim 26, wherein said subject is a human.

34. (***previously presented***) A method according to claim 26, wherein R^1 is a straight-chained alkyl of 1 to 3 carbon atoms, or a branched chain alkyl of 3 to 6 carbon atoms.

35. (***previously presented***) A method according to claim 26, wherein R^1 is a straight-chained alkyl of 1 or 2 carbon atoms.

36. (***previously presented***) A method according to claim 26, wherein R^2 is phenyl, naphthyl, pyridyl, pyrimidyl, furyl, pyrrolyl, pyrazolyl, indolyl, imidazolyl, benzofuryl, or benzothienyl; each optionally substituted with 1 to 3 substituents the same or different selected from straight-chain alkyl of 1 to 3 carbon atoms, branched-chain alkyl of 3 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, mono- or di-alkylamino in which each alkyl group has 1 to 3 carbon atoms, nitro, amino, cyano, halogen, trifluoromethyl, trifluoromethoxy, and hydroxy.

37. (***previously presented***) A method according to claim 26, wherein R^2 is phenyl, naphthyl, pyridyl, pyrrolyl, indolyl, or benzothienyl; each optionally substituted with 1 to 3 substituents the same or different selected from nitro, amino, cyano, halogen, trifluoromethyl, trifluoromethoxy, and hydroxy.

38. (***previously presented***) A method according to claim 26, wherein R^2 is trifluoromethylphenyl or methoxyphenyl.

39. (***previously presented***) A method according to claim 26, wherein the R^1O substituent is bonded to the 1,4-benzodioxan nucleus at the 8 position.

40. (***previously presented***) A method according to claim 26, wherein R^1 is a straight-chained alkyl of 1 to 3 carbon atoms, or a branched chain alkyl of 3 to 6 carbon atoms and R^2 is phenyl, naphthyl, pyridyl, pyrimidyl, furyl, pyrrolyl, pyrazolyl, indolyl, imidazolyl, benzofuryl, or benzothienyl; each optionally substituted with 0 to 3

substituents selected from straight-chain alkyl of 1 to 3 carbon atoms, branched-chain alkyl of 3 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, mono- or di-alkylamino in which each alkyl group has 1 to 3 carbon atoms, halogen, trifluoromethyl, trifluoromethoxy, and hydroxy.

41. ***(previously presented)*** A method according to claim 26, wherein R^1 is a straight-chained alkyl of 1 or 2 carbon atoms, and R^2 is phenyl, naphthyl, pyridyl, pyrrolyl, indolyl, or benzothienyl; each optionally substituted with a 0 to 3 substituents selected from nitro, amino, cyano, halogen, trifluoromethyl, trifluoromethoxy, and hydroxy.

42. ***(previously presented)*** A method according to claim 26, wherein R^1 is a straight chain alkyl of 1 or 2 carbon atoms and R^2 is trifluoromethylphenyl or methoxyphenyl.

43. ***(previously presented)*** A method according to claim 26, wherein said compound is (*S*)-8-(8-ethoxy-2,3-dihydrobenzo-[1,4]dioxin-2-ylmethyl)-3-naphthalen-2-yl-8-aza-bicyclo[3.2.1] octan-3-ol or a pharmaceutically acceptable salt thereof.

43. ***(previously presented)*** A method according to claim 26, wherein said compound is (*S*)-8-(8-ethoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-3-phenyl-8-aza-bicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.

44. ***(previously presented)*** A method according to claim 26, wherein said compound is (*S*)-3-benzo[b]thiophen-3-yl-8-(8-ethoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-8-aza-bicyclo[3.2.1] octan-3-ol or a pharmaceutically acceptable salt thereof.

45. ***(previously presented)*** A method according to claim 26, wherein said compound is 8-{[(2S)-8-ethoxy-2,3-dihydrobenzo-[1,4]dioxin-2-yl]methyl)-3-pyridin-2-yl-8-aza-bicyclo [3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.

46. (***previously presented***) A method according to claim 26, wherein said compound is 8-{[(2S)-8-ethoxy-2,3-dihydrobenzo-[1,4]dioxin-2-yl]methyl)-3-(3-trifluoromethyl-phenyl)-8-aza-bicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.

47. (***previously presented***) A method according to claim 26, wherein said compound is 8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-3-(2-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.

48. (***previously presented***) A method according to claim 26, wherein said compound is 8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-3-[3-(trifluoromethyl)phenyl]-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.

49. (***previously presented***) A method according to claim 26, wherein said compound is 8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-3-(2-pyridinyl)-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.

50. (***previously presented***) A method according to claim 26, wherein said compound is 3-(1-benzothien-3-yl)-8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.

51. (***previously presented***) A method according to claim 26, wherein said compound is 8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-3-phenyl-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.

52. (***previously presented***) A method according to claim 26, wherein said compound is 3-((2S)-8-methoxy-2,3-dihydrobenzo-[1,4]dioxin-2-ylmethyl)-8-naphthalen-2-yl-3-aza-bicyclo[3.2.1]octan-8-ol or a pharmaceutically acceptable salt thereof.